Chronic Diabetes Followed by Chronic Cerebral Ischemia Induced by Bilateral Carotid Artery Ligation in Arteriosclerotic Versus Nonarteriosclerotic Rats

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Abstract: Chronic Diabetes Followed by Chronic Cerebral Ischemia Induced by Bilateral Carotid Artery Ligation in Arteriosclerotic Versus Nonarteriosclerotic Rats

Male and female, arteriosclerotic (breeder) and nonarteriosclerotic (virgin), Sprague-Dawley rats were made severely diabetic with alloxan. Two weeks later experimental animals had both carotid arteries ligated to induce a state of acute cerebral ischemia. After six weeks of cerebral ischemia either with or without severe diabetes the animals were killed. Animals which survived either the acute induction of diabetes or cerebral ischemia did not manifest any new episodes of cerebral ischemia. Subjects with combined diabetes and cerebral ischemia manifested the greatest loss in body weight, adrenal hypertrophy and thymus gland involution, increased levels of serum CPK and SGOT, but decreased SGPT and LDH, hyperglycemia and hypertriglyceridemia, and the most extensive cerebral edema. It is suggested that diabetic rats may have a greater predilection toward cerebrovascular accidents because the diabetic state contributes not only to an exacerbation of atherosclerosis, but also complicates any condition of cerebrovascular ischemia by creating extracerebral edema.

Additional Key Words: triglyceride free fatty acids CPK SGOT SGPT LDH glucose cholesterol compound B edema

It is not known if either hyperglycemia or hyperlipidemia is directly responsible for the premature vascular degenerative changes which occur in diabetic patients. It is clear, however, that diabetic patients are particularly prone to the development of arteriosclerosis, hypertension, myocardial infarction, and cerebrovascular disease. Hyperglycemia and hypertension and arteriosclerosis are the two factors most commonly incriminated as contributors to the pathogenesis of cerebrovascular disease.

We have at our disposal repeatedly bred male and female rats in which hyperglycemia, hyperlipidemia, hypertension, and arteriosclerosis spontaneously develop. There is an intriguing sex dichotomy in that although the male breeder manifests relatively innocuous or microscopic lesions of the aorta, he dies significantly earlier than the female breeder, most often due to myocardial infarction. Although the female breeder incurs severe, calcific, grossly visible aortic sclerosis, commonly reaching up into her carotid arteries, making them kinked, tortuous, and aneurysmatic, she nonetheless survives significantly longer than her male breeder counterparts.

Since diabetes contributes to premature vascular disease and is alleged to contribute to cerebrovascular disease, we induced severe alloxan diabetes in animals having no pre-existing arterial disease (virgins) and in others with pre-existing arterial disease (breeders) to determine whether chronic diabetes would exacerbate cerebral ischemia and to elucidate any differences in the reactions of nonarteriosclerotic versus arteriosclerotic animals to chronic, severe diabetes followed by and combined with chronic cerebral ischemia.

Methods

As many as 2,500 male and female, virgin and breeder, Sprague-Dawley rats were used in order to provide for sufficient survivors, i.e., from previous experience we could anticipate a high mortality rate due to the acute cerebral ischemia of carotid artery ligation and to the severe diabetes induced by alloxan. Male and female virgin rats, comparable in age to the breeder rats, were used as subjects free of arterial disease. Twenty-four of each of the four basic types of animals described previously were killed at the outset of the experiment to provide baseline levels for all the
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parameters measured, i.e., males versus females, arteriosclerotic versus nonarteriosclerotic subjects. A similar, larger group of animals had a single-stage bilateral carotid artery ligation to induce cerebral ischemia. The animals were anesthetized with secobarbital (Seconal). The same surgical procedure described earlier, was followed. Most of the animals which died did so within 15 to 30 minutes of bilateral ligation after having convulsed violently and having manifested extensor rigidity of all extremities. This group of animals received no additional treatment and was used to test the effect of chronic cerebral ischemia alone. All of the remaining experimental animals were starved for 18 hours and then given a single subcutaneous injection of 10 mg of alloxan (Eastman Kodak) per 100 gm body weight to make them severely diabetic. No ameliorative treatment, e.g., insulin, was given. After two weeks of severe diabetes, half of the animals had a single-stage bilateral carotid artery ligation, and the remaining half of the diabetic animals had a sham operation. After six weeks of cerebral ischemia both the control and experimental animals were killed by decapitation to avoid the stress of anesthesia. During the entire eight-week course of this experiment, all of the subjects were provided food and drink ad libitum, except for the animals starved for an 18-hour period, and were housed in our Research Animal Colony in which light, air, temperature and humidity were carefully controlled and monitored.

Blood was spun in a refrigerated centrifuge and the serum was frozen and stored until the time of analysis. The same automated techniques (Auto-analyzer: Technicon) used in our previous reports were used to measure: creatine phosphokinase (CPK), glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), triglycerides, free fatty acids, total cholesterol and glucose. In addition, serum corticosterone (compound B), the main adrenal cortical steroid of the rat, was measured.

At autopsy, each animal was carefully examined for any evidence of cerebral or cardiovascular disease. The sites of carotid artery ligation also were carefully checked; animals showing questionable ligation were discarded. All of the alloxan-treated animals were severely diabetic. Pertinent tissues were saved for histopathological analyses using the same stains and methods described previously.

The biochemical data were analyzed statistically using the analysis of variance method or Student's t-test prescribed by Snedecor and Cochran. P values greater than 0.05 were considered to be not significant.

Results

GENERAL OBSERVATIONS

Within two hours of the single injection of alloxan all animals manifested copious quantities of sugar in their urine. Within 24 hours all of the animals were hyperglycemic and hyperlipidemic and had severe ketosis. Virtually all of the animals which survived this crucial three-day to four-day period survived for the following two weeks despite their severe, unremitting diabetes.

When these diabetic animals had bilateral carotid artery ligation, food and water consumption became drastically reduced despite severe diabetes. The sham-operated diabetic rats were consistently and overtly polyphagic, polydipsic and polyuric. After three to four days, however, the carotid-artery-ligated diabetic rats resumed their intense consumption of food and water, e.g., 60 gm of food (commercial rat chow) per day, 12 oz of water per day per animal. Many of the animals died when the second carotid artery was ligated. However, as the animals began to recover from the relatively deep anesthesia required for bilateral carotid artery ligation, they promptly displayed Horner's syndrome, blanching of both eyes, violent convulsions, extensor rigidity, paraplegia or death. Animals which died at this stage of the experiment manifested a recurrence of severe, fatty stenosis of the liver, and 28% of the arteriosclerotic male breeder rats which died exhibited grossly visible myocardial infarction despite the fact that none of them displayed any evidence of grossly visible aortic sclerosis versus an incidence of 78% of grossly visible aortic sclerosis in female breeders which died at this time.

During the ensuing six weeks, except for marked progressive emaciation and ketosis and persistent Horner's syndrome, paraplegia and miscellaneous neurological sequelae, only an occasional animal died.

GRAVIMETRIC OBSERVATIONS

Male and female breeder rats in which spontaneous hyperglycemia, hyperlipidemia, hypertension and arteriosclerosis develop are characteristically obese and are, on the average, 100 gm heavier than their virgin counterparts (fig. 1). Animals which had bilateral carotid artery ligation alone did not manifest any statistically significant changes in body weight compared to control animals. However, all of the animals made diabetic with alloxan manifested intense catabolic reduction in body weight despite their polyphagia (fig. 1). Animals which had chronic diabetes and chronic cerebral ischemia showed the most severe losses in body weight (fig. 1), and conversely the most substantial increase in adrenal glandular weight (fig. 2). The thymus gland was greatly involuted in these animals in parallel with their manifest adrenal hyperplasia (fig. 3). Heart weights were reduced and kidney weights were increased in the diabetic animals with cerebral ischemia. The weight of the testes was greatly reduced in all of the diabetic animals (P < 0.001) with no discernible difference between those with or without cerebral ischemia. The

*Animals which had bilateral carotid artery occlusion only showed no statistically significant changes in body or organ weights or serum biochemistry when compared to the intact controls at the close of the eight-week experiment. Therefore, the data gathered for this group are not depicted in figures 1 to 12, for the sake of clarity. However, it should be emphasized that we have established that acute bilateral carotid artery occlusion in nonarteriosclerotic virgin and arteriosclerotic breeder rats will definitely elicit marked changes in body and organ masses, dynamic changes in serum biochemistry, concomitant with the acute signs of severe cerebral ischemia. Apparently, these dynamic alterations became normalized during the six-week convalescence period.

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Changes in the final body weight of six-month old nonarteriosclerotic, male and female virgin rats compared with six-month old arteriosclerotic, male and female breeder rats after eight weeks of diabetes with or without cerebral ischemia. The experimental animals first had severe alloxan diabetes for two weeks. Nonarteriosclerotic and arteriosclerotic rats had bilateral carotid artery ligation and some rats with alloxan diabetes also were exposed to sham bilateral carotid artery ligation. (The data from these latter two groups were not different [by statistical analyses] and therefore are omitted from figures 1 to 12.) The arteriosclerotic and nonarteriosclerotic animals remained severely diabetic during the remaining six weeks, except that one group had cerebral ischemia plus diabetes as a result of bilateral carotid artery occlusion. The height of each column denotes the mean and standard error for a given group. The number of samples used for each determination is given in parentheses at the top of each column. Figures 2 to 12 are based on this same protocol.

ovaries were less severely reduced in size (P = < 0.001) in all of the diabetic subjects and, again, with no statistically significant differences between animals with and without cerebral ischemia.

PATHOPHYSIOLOGICAL CHANGES IN THE SERUM

Enzymes

Creatine Phosphokinase (CPK). The CPK levels were elevated in all of the alloxan diabetic animals and particularly in those with bilateral carotid artery occlusion (fig. 4). Animals with pre-existing arteriosclerosis (breeders) did not exhibit any unusual increase in CPK levels compared to those without vascular disease.

Glutamic Oxaloacetic Transaminase (SGOT). Similarly, SGOT levels were greatly elevated in all of the diabetic animals and, with the exception of the

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male breeders with pre-existing microscopic arterial disease, the SGOT levels were significantly elevated in those which had bilateral carotid artery occlusion (fig. 5).

Glutamic Pyruvic Transaminase (SGPT). The SGPT levels were greatly increased in most of the diabetic animals except the female breeders with grossly visible arteriosclerosis (fig. 6). However, there was an unexplainable but statistically significant reduction in SGPT levels in all animals with diabetes and bilateral carotid artery occlusion. Again, the arteriosclerotic female breeders were the exception and manifested no significant differences due to diabetes or diabetes combined with carotid artery occlusion (fig. 6).

Lactic Dehydrogenase (LDH). The LDH levels became greatly reduced with chronic severe diabetes but were even further reduced when the regimen of bilateral carotid artery occlusion was superimposed upon the chronic diabetes (fig. 7).

Carbohydrate

Glucose. All of the alloxanized animals were definitely hyperglycemic throughout the eight-week course of the experiment. Although intact arteriosclerotic breeder rats are characteristically hyperglycemic (fig. 8), their response to the diabetes-inducing effects of alloxan, in terms of hyperglycemia, was as severe as
that observed for the nonarteriosclerotic and previously non-diabetic virgin rats. Again, the surgical maneuver of bilateral carotid artery ligation elicited an even greater state of hyperglycemia (fig. 8).

**Lipids**

**Triglycerides.** Circulating lipid levels also reflected some distinct metabolic responses differentiating the effects of diabetes alone versus diabetes plus carotid artery occlusion. As expected, serum triglyceride levels increased in response to the induced hyperglycemia, except in the case of the arteriosclerotic female breeder rats (fig. 9). However, a very striking and statistically significant ($P < 0.001$) hypertriglyceridemia was observed in all animals which had the combined conditions of diabetes and carotid artery occlusion (fig. 9).

**Free Fatty Acids.** Despite the clear-cut exacerbation of hypertriglyceridemia with the introduction of diabetes and then diabetes plus carotid artery occlusion, the pattern of change in free fatty acids was puzzling. All of the diabetic animals manifested the expected increase in free fatty acid levels. However, the diabetic subjects with both carotid arteries ligated all displayed a statistically significant ($P < 0.001$) decrease in their serum free fatty acid levels (fig. 10), so that they were not too different from the control or intact animals.

**Cholesterol.** The serum cholesterol changes were more erratic but followed, in general, the pattern of change observed for the free fatty acids. Only the nonarteriosclerotic virgin rats displayed the expected
hypercholesterolemia normally associated with severe diabetes, whereas the arteriosclerotic male and female breeder rats actually showed significantly reduced levels of circulating cholesterol despite the fact that intact breeder rats are characteristically hypercholesterolemic (fig. 11). As in the case of the free fatty acids, the circulating levels of cholesterol were reduced in animals with carotid artery occlusion and diabetes combined (fig. 11).

Adrenal steroids
Corticosterone (Compound B). Female rats have higher levels of compound B than male rats. Although repeatedly bred rats are hyperadrenocorticoic initially, they eventually produce less compound B (fig. 12). The induction of chronic diabetes with alloxan resulted in greatly reduced compound B levels (P = < 0.001), i.e., compared to controls. However, in most of the groups the combined condition of diabetes and carotid artery occlusion was associated with the restoration of compound B levels, almost to normal (fig. 12).

GROSS AND MICROSCOPIC PATHOLOGY
General
After eight weeks, when the experiment was terminated, 47% of the male breeder rats with diabetes plus bilateral carotid artery occlusion manifested gross evidence of myocardial infarction (fig. 13), a 19% increase in the incidence of myocardial infarction from the time of surgical ligation six weeks earlier. None of the other animals displayed grossly evident myocardial infarction. None of the male and female virgin rats or the male breeder rats displayed evidence of grossly visible aortic sclerosis. Eighty-four percent of the female breeders exhibited grossly visible aortic sclerosis with a definite increase in the usual severity of aortic sclerosis, i.e., 60% of those with grossly visible aortic sclerosis were "moderate," 20% were "severe," and the remaining 20% were "minimal." This increase in severity of aortic sclerosis was best correlated with the diabetic state per se.

Carotid arteries
The ligature sites remained intact in all of the subjects. It was apparent, by gross inspection, that the carotid arteries of male and female breeder rats with pre-existing arteriosclerosis were dilated, aneurysmal and thrombosed, proximal and distal to the site of ligature,* male breeder rats do not exhibit grossly visible sclerotic plaques of their aorta, although, in some cases, grossly visible advanced lesions can be found in the most proximal portions of the common iliac arteries. Female breeders with no grossly visible aortic sclerosis are classified as "clear." (However, the latter almost invariably will have microscopic aortic lesions.) Those with grossly visible aortic sclerosis confined to the abdominal aortic segment only are classified as "minimal," those with plaques in both the abdominal and aortic arch segments as "moderate," and those with plaques in the arch, thoracic, and abdominal aortic segments as "severe."
High-power view of the myocardium of a male breeder rat having the combined effects of chronic diabetes and cerebral ischemia. The light-gray area is a recently healed infarct consisting of fibrotic material and little or no white blood cells. The darker gray bundles are surviving cardiac muscle cells. H & E, × 150.

in direct contrast to the nonarteriosclerotic virgin rats (figs. 14 and 15). Again, no correlation could be drawn between the surgical maneuver of carotid artery ligation versus alloxan diabetes, but the induction of
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Severe diabetes did cause definite exacerbation of the severity of arteriosclerosis, particularly in the carotid arteries. Cartilaginous metaplasia, intimal fibrosis and medial mucopolysaccharide accumulation (fig. 16) as well as osteoid formation (fig. 17) were frequently encountered in the carotid arteries. The arteriosclerosis extended out into the smaller branches of the carotid arteries with the degenerative change consisting of intimal accumulation of a calcium: mucopolysaccharide admixture and thickening, elongation and fragmentation of the internal elastica (fig. 18). Many of the most distal cerebral arteries exhibited intraluminal aneurysmal outpouching of the intima and internal elastica (fig. 19).

Adrenal and thymus glands
All of the treated animals had hypertrophied hemorrhagic adrenal glands and severely involuted thymi. Histopathological examination of lipid-stained frozen sections of the adrenal glands demonstrated patchy clumping of lipid in some foci surrounded by a more even distribution of lipid throughout all of the zones of the adrenal gland. All of the capillaries in the z. fasciculata and reticularis were greatly dilated. This pattern of adrenal histopathology was directly related to the condition of diabetes, not to the cerebral ischemia.

Liver and kidney
All of the animals subjected to diabetes plus bilateral carotid artery ligation displayed persistent and severe fatty infiltration of the liver (fig. 20), whereas animals with diabetes only, despite severe hyperlipidemia, had slightly fatty livers only. All of the diabetic animals, with or without carotid artery ligation, manifested renal pathology of some kind ranging from arteriolosclerosis to arteriosclerosis, vacuolization of tubules, glomerular hyperplasia and glomerulosclerosis. In some cases the parietal layer of Bowman’s capsule was greatly thickened and intensely
Common carotid artery of an arteriosclerotic female breeder rat made severely diabetic for eight weeks. The lower curvature displays extensive cartilaginous metaplasia; the upper curvature displays overt bone formation. This segment was taken just below the bifurcation of the artery into the external and internal branches. H & E. X 50.

hasophilic. Bowman’s space contained an unusual frothy exudate of a protein-carbohydrate-lipid mixture while the glomerulus was thickened, shrunken and hyalinized (fig. 21).

Brain
All of the animals which had carotid artery ligation exhibited extensive and grossly visible cerebral edema. In addition, most of them also displayed multiple foci of ischemia, hemorrhage and necrosis. These gross observations were confirmed histopathologically. Unlike our findings in animals which had acute carotid artery occlusion, these animals with chronic carotid artery occlusion displayed no or few foci of recent necrosis, i.e., microscopic examination of the brain sections indicated that the foci of necrosis had probably occurred at the time of acute occlusion. The most striking finding was the appearance of unusually severe edema, atheromatous occlusion, peri-arterial white blood cell infiltration (fig. 22) in all oxan diabetic animals with surgically induced cerebral ischemia; animals with carotid artery ligation alone had little or no evidence of edema at the close of the experiment despite numerous foci of cerebral necrosis. Animals with diabetes alone did not develop any cerebral degenerative changes.

Discussion
The most salient feature of this investigation is that diabetes causes a definite exacerbation of vascular disease in rats as it does in humans and that the large arteries in the neck and their smaller branches in the head are particularly susceptible to vascular degenerative changes. Further, the surgical regimen of bilateral carotid artery occlusion (although causing definite cerebrovascular ischemia and infarction) manifests most of its effects by acute ischemia, infarction, and alteration of several specific metabolic parameters, e.g., lipids and steroids, whereas diabetes, regardless of the presence or absence of severe diabetes. These definitive metabolic changes, with or without diabetes, are observable on a chronic basis as well. Diabetes, in the rat, hastens and extends the anatomical distribution of vascular disease and aggravates any existing cerebral edema.

It is of interest that the stressful conditions of acute myocardial ischemia (induced by isoproterenol) and acute cerebrovascular ischemia (induced by bilateral carotid artery ligation) caused temporary hepatic steatosis. It is important to emphasize the fact that only those animals having diabetes plus bilateral carotid artery ligation exhibited severe and persistent hepatic steatosis throughout the eight-week course of the experiment. That is, the combined regimen of diabetes and cerebral ischemia imparted some definitive and persistent metabolic condition pertinent to abnormal lipid metabolism.

The very marked adrenal hyperplasia and significant increase in adrenal weight concomitant with equally severe thymic involution but reduced compound B production is a confirmation of the fact that diabetes interferes with proper adrenal steroidogenesis. The fact that diabetes plus carotid artery ligation also caused an exacerbation of this adrenal hypertrophy and thymus gland involution suggests that carotid artery ligation contributes, per se, in some way to this intense adrenocortical stimulation. One possible explanation is the fact that bilateral carotid artery occlusion has been shown to cause increased production of 17-hydroxycorticoids.

The special effects of combined diabetes and cerebral ischemia were also reflected by changes in several biochemical parameters. With a few exceptions, the serum CPK and SGOT levels were exceptionally elevated, whereas the SGPT and LDH levels were depressed in those animals having the combined effects of diabetes and cerebral ischemia. It is clear that the CPK levels would be elevated because of the cerebral ischemia and necrosis, and the greatly elevated SGOT levels would reflect the advanced fatty infiltration of the liver, but it is not clear why the enzymes SGPT and LDH should be depressed. The fact that the arteriosclerotic rats did not show any unusual enzyme changes is not unexpected since we have found that arteriosclerotic rats having acute myocardial ischemia paradoxically survive better and respond...
with less excursion of their serum enzymes, lipids, etc., compared to nonarteriosclerotic subjects. It is understandable why diabetic rats manifested hyperglycemia and hypertriglyceridemia, but it is an enigma why they showed decreased free fatty acids and cholesterol levels, specifically, when confronted with the additional insult of cerebral ischemia.

Earlier, we had alluded to the fact that male breeder rats are particularly susceptible to myocardial infarction. It would be pertinent to underscore the fact that 47% of the male breeder rats having diabetes plus cerebral ischemia displayed evidence of myocardial infarction by both gross and microscopic inspection. It is becoming more apparent that patients with an acute myocardial infarct, diabetic or otherwise, may simultaneously suffer cerebral ischemia or vice versa. It has been suggested that carotid artery occlusion may condition the myocardium toward ischemic necrosis because it elicits increased production of glucocorticoids, increased angiotensin, and other hemodynamic alterations conducive to myocardial infarction. Melville et al. have suggested that the cardiac ischemia and arrhythmia associated with cerebrovascular accidents is due to abnormal hypothalamic activity. We are particularly intrigued with this latter concept because, although we have not yet been able to find specific evidence of hypothalamic damage in our arteriosclerotic breeder rats, they do display varying degrees of cerebral arterial disease. We have found evidence of abnormal pituitary trophic hormone release in these rats due to defective hypothalamic releasing factor production and release, e.g., ACTH, prolactin and LH (to be published).

Perhaps the most salient feature of this experimental investigation pertains to the changes observed within the main carotid arteries, their branches and the condition of cerebral edema. The dichotomous response of the carotid arteries of nonarteriosclerotic virgin rats versus arteriosclerotic breeder rats at the site of injury (carotid artery ligation) illustrates the disparate response of the arterial wall to a noxious stimulus. Similarly, the excraba-
cerebrovascular impairment through its well-known acceleration of the process of arteriosclerosis. Even more cogent to the pathogenesis of cerebral impairment, in these animals, is our finding of most severe cerebral edema in the case of those animals which were simultaneously diabetic and had cerebral ischemia. Patients and animals with severe diabetes and ketoacidosis also have cerebral edema, which causes increased intracranial pressure and increased debilitation. In these experiments, only the animals with diabetes plus carotid artery ligation had severe cerebral edema. It may be that bilateral carotid artery occlusion, by virtue of its ability to induce increased production of glucocorticoids, angiotensin and aldosterone, may have contributed to the cerebral edema associated with cerebrovascular problems.

In this same connection, Kannel et al. have made the very provocative observation that diabetic patients, particularly those who were insulin dependent, had a significantly greater predilection to have congestive heart failure than those whose diabetes was controlled with oral drugs. These investigators emphasize that the increased incidence of congestive heart failure was not correlated with hypertension, hyperlipidemia, obesity or coronary atherosclerosis but to a specific cardiomyopathy related to the patient's ketosis or severity of diabetes. The observance of a proclivity toward increased cerebral edema and congestive heart failure coincident with severe, poorly controlled diabetes is intriguing. Therefore, it is suggested that the combined effects of arteriosclerosis and diabetes...
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Cerebral artery of animal described in figure 21 showing an occluded artery surrounded by hemorrhage and white blood cells. Note the extensive cerebral edema. H & E, ×75.

contribute to generalized and persistent cerebral edema which conditions the subject toward premature and inexorable cerebral damage as cerebral arterial disease and ischemia worsen and cerebral metabolism becomes compromised.

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